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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/904,786	07/12/2001	Avi Ashkenazi	10466/84	3015

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EXAMINER	
BASI, NIRMAL SINGH	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 05/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/904,786	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Nirmal S. Basi	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Upon further review the finality of the rejection of the last Office action is withdrawn. The claims are newly rejected for the reasons given below.

2. Appeal Brief filed 3/14/06 has been entered.

3. Claims 1-38 and 44 are cancelled and 39-43 are pending.

Claim Rejections Under 35 USC § 101 and 35 USC § 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 39-43 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. The claims are directed to isolated antibody that specifically binds to the polypeptides of SEQ ID NO:290, referred to in the specification as PRO335. The specification also generally asserts that all of the disclosed PRO335, based on the MLR reaction, stimulates proliferation of lymphocytes and is useful therapeutically where enhancement of an immune response is beneficial; however, this asserted use does not meet the three-pronged requirement of 35 U.S.C. 101 regarding utility, namely, that the asserted utility be credible, specific and substantial. Therefore PRO335 polypeptide,

antibody that binds PRO335 polypeptide or the nucleic acid encoding PRO335 polypeptide do not have any specific and substantial utility, or a well established utility, as determined according to the current Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday, January 5, 2001.

Applicant asserts that Example 74, page 208 of the specification at line 27, supports utility of the claimed invention. Example 74 of the specification is stimulatory activity in a mixed lymphocyte reaction (MLR) assay. However, the ability of a protein to stimulate lymphocyte proliferation in this assay does not support a specific and substantial utility for the claimed invention. The ability to stimulate or inhibit lymphocyte proliferation in the MLR assay is an artificial *in vitro* system and does not provide for what specific conditions or for which specific diseases the claimed invention would predictably function. The assertion that the claimed invention could be useful for the treatment of conditions where the enhancement of the immune response would be beneficial is not specific since there are many such conditions, and it is not predictable of which conditions the claimed invention may function, if any. The claimed utility is not a substantial utility because there is no information regarding the correlation of the MLR results to any real-life diseases. There is no information regarding what subsets of immune responses, immune cell types etc. are targeted by compounds with activities disclosed in MLR assay.

Mixed lymphocyte culture (MLC) is a special case of antigen stimulation in which T lymphocytes respond to foreign histocompatibility antigen on unrelated lymphocytes or monocytes. MLC is a functional assay of cellular response to

stimulatory determinants associated predominantly with HLA class II molecules. A single genetic locus or region, known as HLA, controls the MLC reactivity. The MLC assay recognizes disparate HLA class II molecules and the resulting T-cell activation, which is thought to represent an *in vitro* model of the afferent arm of the *in vivo* allograft reaction. The degree of reactivity observed correlates with the degree of antigenic disparity between responding and stimulating cells. Briefly, when the lymphocytes of 2 HLA-disparate individuals are combined in tissue culture, the cells enlarge, synthesize DNA, and proliferate, whereas HLA-identical cells remain quiescent. Since both cells will normally proliferate, a one way test is used to monitor the response of a single responder cell by inactivating the stimulator cell by radiation or drugs in order to inhibit DNA synthesis of the stimulator cell. The proliferation is driven primarily by the differences in the class II HLA antigens between the 2 test cells (or individuals). This reaction is not predictive of general responses of the immune system because, *in vivo*, activation of a lymphocyte is controlled not only by antigen binding but also by interactions with other cells. All T cells must cooperate with antigen-presenting cells, whereas B cells and cytotoxic T cells depend on helper T lymphocytes. These interactions either require direct surface-to surface contact or are mediated by cytokines that act only over extremely short distances. Because of this interdependence, lymphocyte activation occurs commonly and efficiently in the secondary lymphoid organs, where lymphocytes, antigens, and antigen-presenting cells encounter one another at close quarters. See pages 30-31, 208-

209, 246-247 of "Basic and Clinical Immunology," 1994. See also, "Manual of Clinical Laboratory Immunology," 6th Edition at pages 1164-1166.

Kahan clearly states that no *in vitro* immune assay predicts or correlates with *in vivo* immunosuppressive efficacy; there is no surrogate immune parameter as a basis of immunosuppressive efficacy and/or for dose extrapolation from *in vitro* systems to *in vivo* conditions (Cur. Opin. Immunol. 4: 553-560, 1992; see entire document, particularly page 558, column 2). Piccotti et al. (Transplantation 67: 1453-1460, 1999) demonstrate that IL-12 enhances alloantigen-specific immune function as determined by MLC, but this result in vitro does not result in a measurable response *in vivo* (i.e. failure to accelerate allograft rejection) (see page 1459). Campo et al. (Biological Trace Element Res. 79: 15-22, 2001) demonstrate that while zinc suppresses alloreactivity in MLC, it does not decrease T-cell proliferation *in vitro* nor produce immunosuppressive effects *in vivo*. Urso et al. (Cell. Mol. Biol. 41 supplI : s103-112, 1995, cited previously) teaches that zidovudine, which enhanced MLR response, was ultimately in fact immunosuppressive. Kond et al. (Immunology 79 : 459-464, 1993, cited previously) teaches that TGF-beta has both immunosuppressive and immuno-enhancing in such *in vitro* assays, but is immunosuppressive in vivo. Therefore, the MLR assay, which is art recognized for determining histocompatibility, does not appear to be predictive of general immune responses in vivo.

Additionally, difficulties arise in quantification when using MLC as a test for T cell function due to variations in stimulator cell antigens that determine the

degree of genetic disparity between stimulator and responder cells. MLC is typically used for determining histocompatibilty in an individual and as a test for immunocompetence of T cells in patients with immunodeficiency disorders. When running the MLC assay for determining histocompatibility for transplantation, autologous controls combining self with irradiated self are necessary to normalize the response of each cell to stimulators. Furthermore, there is known inherent variability of individual cellular responses from day to day which requires performing the entire familial MLC at one time in the case of determining histocompatibility for transplantation (page 246 in "Basic and Clinical Immunology"). When performing the MLC assay, each individual lot of a serum source should be screened for growth support capabilities and possible HLA antibodies (see page 1165 in "Manual of Clinical Laboratory Immunology"). Additionally, the screen should include a control response to a pool of allogeneic cells to measure maximum response and an autologous control to ensure low backgrounds.

Therefore, the MLC (a.k.a. MLR) assay is a measure of alloreactivity of one individual to another individual, rather than a general measure of immune function. This reactivity is governed by the antigenic disparity between the two individuals, which are being compared in the assay. Depending on the individuals being tested, the MLC may indicate stimulation if they are HLA-disparate or the MLC may indicate no stimulation if the individuals are HLA-identical. The ability of the claimed invention to stimulate proliferation in the MLC

assay may not be a general stimulus to lymphocyte proliferation, but rather a reaction to one of the MHC antigens on the responder cell. The instant specification fails to provide sufficient detail of the assay, which was performed and fails to provide any data whatsoever in order for one of ordinary skill in the art to evaluate the conclusion that lymphocyte proliferation was stimulated by the claimed invention. As pointed out above, there are several controls which the art recognizes as being essential for meaningful results for this assay, including autologous controls, a control to determine maximum response, screening for possible HLA antibodies and growth support capabilities. Furthermore, there is known inherent variability of individual cellular responses from day to day, which would clearly dictate the need for internal controls. The specification indicates that CD4-IgG was used as a control, but it is not clear how this would control for background stimulation or provide for a measure of maximal stimulation. Lastly, the specification fails to provide any data or evidence of the results of the assay, therefore, one of ordinary skill in the art cannot evaluate the conclusion. The specification states that "positive increases over control are considered positive", however, this does not indicate that statistical significance must occur for determination of a positive result in the assay. In conclusion, the results of the MLC (a.k.a. MLR) assay do not support a specific and substantial utility for the claimed invention because the assay is not predictive of immune response in general, and one of ordinary skill in the art would not expect a stimulatory effect in the MLC assay to correlate to a general stimulatory effect on the immune system, absent evidence to the contrary.

5. Claims 39-43 are also rejected under 35 U.S.C. 1 12, first paragraph.

Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

6. The rejection of claims 39-43 under 35 U.S.C. 112, first paragraph, as lacking enablement is maintained for reasons of record in the office actions of 8/11/05, 11/17/04, 4/28/04 and 12/19/03.

Applicants argue that the MLR assay is a well accepted and useful assay for identifying immunostimulants and is a widely used proliferative assay of T-cell function and can identify agents that can boost the immune system. Dr. Fong points to IL-12 as such a stimulant and states that a PRO polypeptide that stimulates T-cell proliferation with an activity "at least 180% of control" would find practical utility as an immune stimulant. Applicants submit that PRO335, contributes to stimulating the cellular responses (cellular immunity) rather than the humoral responses, of the immune system and therefore, is not directed to any "particular antigen". Applicant further argues the MLR assay is useful for detecting immunostimulatory activities of molecules like PRO335.

Applicants' arguments have been fully considered but have not been found to be persuasive. No "particular antigen" is identified in the specification; there is no guidance as to how PRO335 could be used to boost the response to any antigen. Current Protocols in Immunology states on p. 3.12.11 that the MLR

"only detects dividing cells instead of measuring true effector T-cell function" and that it is "not clear which T cell function is measured in proliferative assays", and further that "the proliferative response should be used solely as a general indicators of T cell reactivity". Data obtained might variously reflect proliferation of CTL, lymphokine producing T cells, or non-activated bystander cells and will be severely affected by the function of non-T cells. Differences in responsiveness in a proliferative assay in part reflect differences in IL-2 production, according to Current Protocols in Immunology. As has been stated previously, the MLR measures the reactivity of one individual to another and is, as Current Protocols in Immunology states, highly variable. Current Protocols in Immunology in fact describes many variables that must be controlled for. In the instant application, no such controls, such as for maximum response or for the inherent variability of individual responses, are provided. There is no indication of the statistical significance of the results. There are no autologous controls. No correlation is provided to any particular *in vivo* function; there is no guidance to indicate that PRO335 could be used to any therapeutic effect for the treatment of diseases such as cancer or HIV. The references cited by Applicant fail to provide compensatory guidance. Steinman and Thurner et al. (see previous office action) address the utility of dendritic cells but not of a stimulatory MLR. Gubler (see previous office action) describes the identification of the molecule IL-12 but uses the MLR merely to compare activities, not as the basis for describing a molecule as a therapeutically useful immunostimulant. The subsequent research of Peterson et al. (see previous office action) was clearly required to

suggest that the molecule could be used in this fashion. Thus, without further guidance correlating the observed stimulatory activity to a particular, useful property, it would require undue experimentation to use PRO335.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal S. Basi whose telephone number is 571-272-0868. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nirmal S. Basi
Art Unit 1646
5/26/06

GARY B. NICKOL, PH.D.
PRIMARY EXAMINER